The IASLC/ITMIG Thymic Epithelial Tumors Staging Project: proposals for the N and M components for the forthcoming (8th) edition of the TNM classification of malignant tumors

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The IASLC/ITMIG Thymic Epithelial Tumors Staging Project: Proposals for the N and M Components for the Forthcoming (8th) Edition of the TNM Classification of Malignant Tumors

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Abstract: Stage classification is an important underpinning of management of patients with cancer, and rests on a combination of three components: T for tumor extent, N for nodal involvement, and M for more distant metastases. This article details an initiative to develop proposals for the first official stage classification system for thymic malignancies for the 8th edition of the stage classification manuals. Specifically, the results of analysis of a large database and the considerations leading to the proposed N and M components are described. Nodal involvement is divided into an anterior (N1) and a deep (N2) category. Metastases can involve pleural or pericardial nodules (M1a) or intraparenchymal pulmonary nodules or metastases to distant sites (M1b).

Key Words: Staging, Prognosis, Thymoma, Thymic carcinoma, Stage classification

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†††See Appendix 1; ‡‡‡see Appendices 2, 3, and 4; §§§see Appendix 5.

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Stage classification is fundamental to management of patients with cancer because it provides a common language regarding anatomical extent of disease. Progress in thymic malignancy has been slowed by the lack of a universal, clearly defined system. Therefore, the Thymic Domain of the Staging and Prognostic Factors Committee (TD-SPFC) of the International Association for the Study of Lung Cancer (IASLC) and the International Thymic Malignancies Interest Group (ITMIG) sought to develop a TNM stage classification system that would be applicable to both thymoma and thymic carcinoma (TC).[1] This has advantages in being consistent with the general format of the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC) stage classification system. Furthermore, a single system for thymoma and TC provides simplicity, which is important in a rare disease.

Five TNM stage classification systems for thymic malignancies have been previously proposed, but there is no official, widely adopted system.[2] These schemes divide the N component into two to four categories and the M component into two to three categories. Although there are similarities among the N and M categories in some of these systems, there are also differences. The TD-SPFC created specific N and M workgroups to consider what would best serve the needs of the global medical community to inform the 8th edition of the AJCC/UICC stage classification for thymic malignancy. This article reports on the deliberations and outcomes of this process.

METHODS

A general overview of the database used for this analysis and the principles guiding the development of a stage classification system have been described elsewhere.[1,3,4] In summary, a large international retrospective database including more than 10,000 patients overall was developed by the ITMIG and several other organizations (European Society of Thoracic Surgeons,

Japanese Association for Research in the Thymus [JART], Chinese Alliance for Research in Thymoma). The IASLC provided infrastructure and funding to allow an extensive analysis, which was performed by the Cancer Research And Biostatistics group to develop TNM-based, data-driven stage classification proposals to inform the 8th edition of the AJCC/UICC stage classification system. Papers describing details of the T component and the stage grouping are provided elsewhere.[3,4]

Despite the large size of the database, details regarding the N or M status were available in only a subset of the patients. This reflects the fact that advanced thymic tumors are less common, the fact that data on resected patients was more readily available for inclusion in the database, and that retrospective data was most often collected according to traditional staging systems which often did not discriminate among details of N and M involvement. The vast majority of data with sufficient detail comes from JART. This organization and the country of Japan have had a long-standing commitment to gathering detailed data regarding extent of disease of thymic and other cancers. This was invaluable to the IASLC/ITMIG stage classification project (Fig. 1). Input was specifically sought out from the TNM committee of the Japan Lung Cancer Society (Jun Nakjima, Masaki Hara, Kazuya Kondo, Meinoshin Okumura, Yoshihiro Matsuno, Motoki Yano), because of the work that this group and others in Japan have done to investigate the impact of nodal involvement in thymic malignancies.

The limited amount of detailed data precluded being able to assess whether there were statistically significant differences in the outcomes of various cohorts. The analysis was based primarily on a visual assessment that suggested a difference, similarities of the N classification to a consensus-based ITMIG/IASLC mediastinal thymic node map,[5] similarities of the M classification to the Masaoka and Masaoka-Koga stage classification systems (representing the two systems in most common use), practical considerations relative to the conduct of surgery for thymic malignancies and a consensus opinion about what was worthwhile to distinguish. Details of the statistical methods that were used where possible are described elsewhere.[3]

A collaborative process was conducted by ITMIG in conjunction with the TD-SPFC to develop a node map for thymic malignancies.[5] This workgroup considered anatomical factors, surgical aspects, and existing node mapping systems (i.e., for lung, head, and neck cancers and previously proposed systems for thymic malignancy) to develop a proposed map. The product of this effort was remarkably similar to what the TD-SPFC group developed through analysis of the available data. The ITMIG node map workgroup and the TD-SPFC discussed and coordinated their efforts to produce a final node map and an N classification system that were congruent.

PROPOSED N COMPONENT CLASSIFICATION

The proposed N classification is shown in Table 1. The TD-SPFC proposes dividing nodal involvement into an anterior (perithymic, N1) and a deep (N2) category, consistent with the definitions of these regions in the ITMIG/IASLC node map (Fig. 2).[5] The anterior region extends from the hyoid bone to the diaphragm, bounded anteriorly by the sternum, posteriorly by the trachea (neck) and pericardium (chest), and

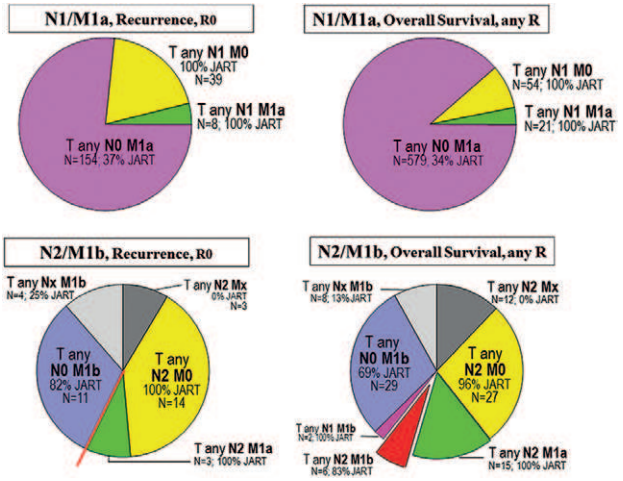


FIGURE 1. Evaluable patients for the N and M component analysis. Diagram of evaluable patients available for analysis, by N and M characteristic, with the proportion contributed by the Japanese Association for Research in the Thymus (JART).

TABLE 1. N, M Descriptors

Category	Definition (Involvement of)[a]
N0	No nodal involvement
N1	Anterior (perithymic) nodes
N2	Deep intrathoracic or cervical nodes
M0	No metastatic pleural, pericardial, or distant sites
M1	
a	Separate pleural or pericardial nodule(s)
b	Pulmonary intraparenchymal nodule or distant organ metastasis

[a]Involvement must be pathologically proven in pathologic staging.

laterally by the medial border of the carotid sheaths (neck) and the mediastinal pleura (chest). The distal boundaries of the deep region are defined by the medial edge of the trapezius muscle (neck) and the pulmonary hila (chest) laterally and the esophagus and vertebral column posteriorly. The deep region includes paratracheal, subcarinal, aortopulmonary window, hilar, jugular, and supraclavicular nodes. Involved nodes outside these regions (e.g., axillary, subdiaphragmatic) are outside the N category and considered a distant metastasis. Further details are provided elsewhere.[5]

The JART has conducted by far the best analysis of the incidence and location of node metastases from thymic malignancies.[6] Lymph node metastases were seen in 2% of 1064 thymomas, 27% of 183 TCs, and 28% of 40 thymic neuroendocrine tumors (NETT). These node metastases were seen most often in what corresponds to the region defined here as N1: of node-positive patients 89% with thymoma, 69% with TC, and 91% with NETT had involvement of N1 nodes, and 26% of thymoma, 30% of TC, and 45% of NETT had involvement of N2 nodes (most with N2 involvement also had N1 involvement).[6]

In the ITMIG/IASLC database, a limited number of patients had sufficient detail reported to allow evaluation of outcomes for the proposed anterior and deep nodal regions.

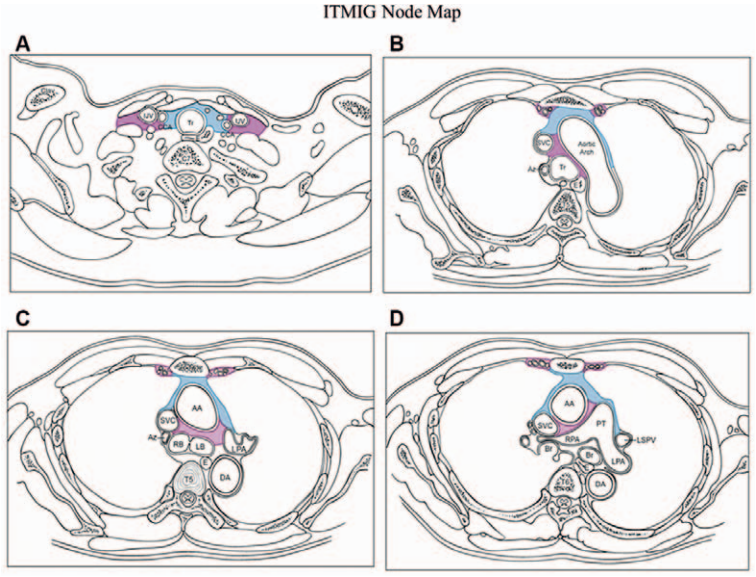


FIGURE 2. ITMIG /IASLC Lymph Node Map. Anterior and deep node regions as depicted on axial images. Anterior region (*blue*); deep region (*purple*). For further detail see Bhora et al.[5] (*A*) Thoracic inlet; (*B*) paraaortic level; (*C*) AP window level; (*D*) carina level. AA, ascending aorta; Az, azygos vein; CCA, common carotid artery; BR, bronchus; Clav, clavicle; DA, descending aorta; E, esophagus, IJV, internal jugular vein; LB, left main bronchus; LPA, left pulmonary artery; LSPV, left superior pulmonary vein; PT, pulmonary trunk; RB, right main bronchus; RPA, right pulmonary artery; SVC, superior vena cava; Tr, trachea.

Such detailed data were almost exclusively available from the patients contributed by JART. Nodes listed as N1 in JART correspond well with anterior intrathoracic (N1) nodes in the ITMIG/IASLC scheme; JART N2 nodes correspond to deep intrathoracic nodes in the ITMIG/IASLC scheme. These approximations were used to assess the outcomes of node involvement in the TD-SPFC classification proposal. There were few patients (n = 17) with involvement of neck nodes (JART N3) in the ITMIG/IASLC database. Following discussion with the curators of the JART database, these were felt in general to correspond to deep cervical nodes (N2 in the ITMIG/IASLC map). Their outcome did track with that of intrathoracic N2 nodes (5-year OS, R any was 44% for JART N2 and 40% for JART N3). Hence the JART N3 nodes were included in the Cancer Research And Biostatistics analyses together with other ITMIG/IASLC N2 nodes. A priori it was thought that data on all patients regardless of R status (i.e., R any) would be most relevant, since an R0 cohort would be more selected and less applicable to clinical staging.

Examination of the available data shows that OS among patients with any R status is better for the N1 versus the N2 category (5-year survival 69% versus 47%). This is more difficult to assess in R0 resected patients, because there are few in the N2 R0 groups; OS appears to be worse for N2 versus N1 but the rate of recurrence is similar (Fig. 3). However, none of the differences reached statistical significance (including OS in the R any cohort). The overall rates of death (Table 2) also demonstrate that N2 is worse than N1 among R any patients. Overall rates of recurrence are difficult to assess because there are few R0 patients in the N2 category, and even fewer in which recurrence information was available.

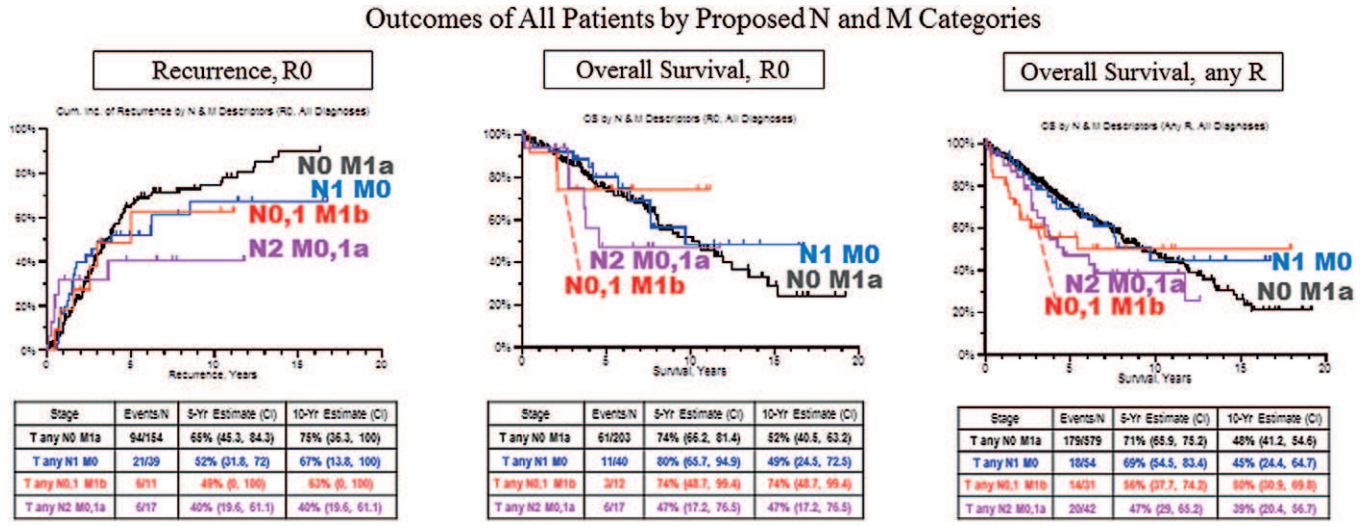
The TD-SPFC proposes to distinguish N1 from N2 nodes as outlined for several reasons. The speculation that involvement of nodes close to the thymus (N1) signifies less advanced or aggressive disease than involvement of deep (N2) nodes seems plausible. This is borne out at least qualitatively by the data in the ITMIG/IASLC database and by prior JART analyses,[6,7] although the power to detect statistical significance for the difference is limited by the amount of data available. From a practical, clinical standpoint, the separation of anterior and deep regions is appealing because the anterior region nodes would be included in an extended thymectomy, whereas access to the deep region nodes would require extra effort. Furthermore, the separation is similar to what has been used by the JART in previous analyses and corresponds to the ITMIG/IASLC consensus-based node map developed by a parallel process.[5–7] Finally, in the absence of data demonstrating that further subdivision (i.e., N3) distinguishes patients with a different prognosis, it seems that keeping it simpler is better.

Microscopic demonstration of involvement is needed to classify a node as involved by pathologic stage classification. Invasion by direct extension is counted as nodal involvement. There is no data to assess the impact of direct invasion versus a nodal deposit that is separate from the primary tumor. However, the TD-SPFC decided on this definition to be consistent with the IASLC/AJCC/UICC definition for lung cancer.

To stage nodes accurately, ITMIG has proposed that anterior mediastinal nodes be routinely removed along with the thymus and encouraged a systematic sampling of deep nodes when resecting thymomas with invasion of mediastinal structures (pericardium, lung, etc.).[8] For TC, a systematic removal of both N1 and N2 nodes is recommended during curative-intent resection.[8] A study specifically addressing the role of node dissection in TC (37 patients) also suggested that anterior and paratracheal nodes should be routinely dissected, especially when adjacent organs were invaded.[9] A minimum number of 10 dissected nodes were suggested in that study, as this appeared to correlate with better survival.[9]

PROPOSED M COMPONENT CLASSIFICATION

The M component is divided into three categories: M0 if there are no metastatic sites, M1a if there are pleural or pericardial nodules separate from the primary tumor mass, and M1b if there are distant (extrathoracic) metastases or pulmonary



Stage	Events/N	5-Yr Estimate (CI)	10-Yr Estimate (CI)
T any N0 M1a	94/154	65% (45.3, 84.3)	75% (36.3, 100)
T any N1 M0	21/39	52% (31.8, 72)	67% (13.8, 100)
T any N0,1 M1b	6/11	48% (0, 100)	63% (0, 100)
T any N2 M0,1a	6/17	40% (19.6, 61.1)	40% (19.6, 61.1)

Stage	Events/N	5-Yr Estimate (CI)	10-Yr Estimate (CI)
T any N0 M1a	61/203	74% (66.2, 81.4)	52% (40.5, 63.2)
T any N1 M0	11/40	80% (65.7, 94.9)	49% (24.5, 72.5)
T any N0,1 M1b	3/12	74% (48.7, 99.4)	74% (48.7, 99.4)
T any N2 M0,1a	6/17	47% (17.2, 76.5)	47% (17.2, 76.5)

Stage	Events/N	5-Yr Estimate (CI)	10-Yr Estimate (CI)
T any N0 M1a	179/579	71% (65.9, 75.2)	48% (41.2, 54.6)
T any N1 M0	18/54	69% (54.5, 83.4)	45% (24.4, 64.7)
T any N0,1 M1b	14/31	56% (37.7, 74.2)	50% (30.9, 69.8)
T any N2 M0,1a	20/42	47% (29, 65.2)	39% (20.4, 56.7)

FIGURE 3. Outcomes of all patients by proposed N and M categories. Outcomes of all patients with a thymic malignancy of any type. *A*, Cumulative incidence of recurrence, R0 resected patients; (*B*) overall survival, R0 resected patients; (*C*) overall survival, all patients (any R status); point estimates at 5 and 10 years are provided in the tables. There are no statistically significant differences between the curves. CI, 95% confidence interval; Cum. Inc. of Recurrence, cumulative incidence of recurrence; *N*, total number of evaluable patients; OS, overall survival; R0, complete resection; Yr, year.

TABLE 2. Total Proportion of Recurrences or Deaths

	Recurrence, R0		Deaths, R0		Deaths, any R	
	%	Events/*n*	%	Events/*n*	%	Events/*n*
Stage IVa	**59**	**119/201**	**30**	**75/251**	**32**	**209/654**
N1 M0	54	21/39	28	11/40	33	18/54
N0 M1a	61	94/154	30	61/203	31	179/579
N1 M1a	50	4/8	38	3/8	57	12/21
Stage IVb	**49**	**17/35**	**33**	**14/43**	**43**	**43/99**
N2 M0,1a	35	6/17	35	6/17	48	20/42
N0,1 M1b	55	6/11	25	3/12	45	14/31
N2 M1b/X + NX M1b	71	5/7	36	5/14	35	9/26

The total number of recurrences or deaths observed at any time out of the total number of evaluable patients in each category.
R, resection status; R0, complete resection.

intraparenchymal nodules (Table 1). One reason for this three-way separation is that there may be a different mechanism of spread (i.e., local dissemination through the pleural or pericardial space versus hematogenous spread, although this is based on rationale and speculation). It also appears that the extent of dissemination is different, and the implications for treatment are generally viewed as different. Finally, the decision was also based on a visual impression that the outcome curves are different for M1a and M1b (Fig. 3).

The OS among N0 any R patients is better for the M1a versus the M1b category (5-year survival 71% versus 56%, Figure 3), although the differences are not statistically significant. Overall rates of death among R any patients are worse for N0,1 M1b versus N0 M1a cohorts (45% versus 31%, Table 2). The limited data available make outcomes among R0 resected patients difficult to interpret.

The ability to evaluate outcomes for statistical significance was limited given the size of the patient cohorts and by the nature of the database. The database primarily involves surgically resected patients; however, it is likely that the majority of patients diagnosed with M1a and especially M1b involvement from a thymic malignancy are managed nonsurgically. Thus, the resected M1b patients in the ITMIG/IASLC database represent a very selected subset of all M1b patients. Because of these considerations, the TD-SPFC weighed the rationale about the mechanism of spread and potential treatment implications heavily and downplayed the observed outcomes in M1b patients. A stage classification system that is applicable to all patients must take into account patients who are not resectable—at least conceptually and speculatively if data is not available for analysis.

The TD-SPFC evaluated whether there was a difference in outcomes of pleural nodules, pericardial nodules, or intraparenchymal pulmonary nodules. No difference was apparent, although the number of patients with this level of detail was limited. The TD-SPFC also discussed whether pulmonary parenchymal nodules should be classified together with pleural and pericardial nodules. The decision was made to classify pulmonary parenchymal nodules as M1b. This was based primarily on the speculation of the mechanism of spread, and the consistency this afforded with the interpretation of the Masaoka and Masaoka-Koga stage classification systems.[10] The historical classification of pleural nodules together with pericardial nodules was retained (both are considered M1a). There were too few patients to analyze and no clear difference among these groups, although there was a slight suggestion of worse OS for pericardial versus pleural nodules in R any patients).

Examination of the nature of patients included in the M1b cohort reveals that the vast majority of these had pulmonary parenchymal nodules. Those that had other distant sites

of disease but were included in the database are likely a very selected subgroup. It is also likely that many of the patients with pulmonary nodules may have been discovered incidentally at the time of resection; caution is advised in extrapolating these outcomes to patients with preoperatively identified intraparenchymal pulmonary nodules.

The recurrence and survival outcomes of patients with N1 involvement are similar to those of patients with M1a involvement. In addition, the outcomes of patients with N2 and M1b involvement (or both) are similar (Fig. 3, Table 2). The N1 and M1a cohorts were grouped into the stage group IVa and the N2 and M1b cohorts into stage group IVb, as is described elsewhere.[3] However, these similar observed outcomes do not necessarily mean that the biological behavior is the same; factors influencing a propensity for nodal involvement and pleural involvement may be different. The outcomes for thymoma and TC followed similar trends to what was observed for all patients (N1 better than N2, M1a better than M1b, Supplemental Figure 1, Supplemental Digital Content 1, http://links.lww.com/JTO/A656). Therefore, although the number of patients is limited the proposed classification appears applicable to both thymoma and TC. NETT of the thymus were not included in either of these subsets and were too few to be analyzed separately.

DISCUSSION

Development of a uniform stage classification system is a major prerequisite for progress in treatment, particularly in an uncommon malignancy. The lack of an official stage classification has been an impediment which the IASLC/ITMIG initiative set out to address. The proposals defined in this article and the companion papers pave the way for a worldwide uniform system starting with the 8th edition of the stage classification system.[3,4]

A comparison to the five previously proposed TNM classification systems reveals similarities and differences among the N classifications. The Yamakawa–Masaoka and Tsuchiya systems[11,12] defined anterior mediastinal lymph nodes around the thymus as N1, intrathoracic lymph nodes other than anterior mediastinal lymph nodes as N2, and extrathoracic lymph nodes as N3. The WHO and Bedini systems[13,14] defined N3 more specifically as scalene and/or supraclavicular lymph nodes. The Weissferdt–Moran system (for TC)[15] considers only intrathoracic nodes in the N classification. The system proposed by the TD-SPFC is similar (but more detailed and specific) in defining intrathoracic N1 and N2 nodes, but differs in classifying low cervical nodes adjacent to the upper poles of the thymus or slightly further removed (e.g., jugular or supraclavicular nodes) also as N1 and N2, respectively.

The Yamakawa–Masaoka, Tsuchiya, Weissferdt–Moran, and WHO schemes define M1 as hematogenous or distant metastases.[11,12,14,15] In these schemes, pleural or pericardial nodules are classified as T4. The Bedini scheme[13] classifies distant metastasis as M1b. Pleural nodules are designated as M1a if they are posterior to the phrenic nerve and as T4 if they are anterior to the phrenic nerve. The TD-SPFC proposal is to classify separate pleural or pericardial nodules as M1a. This fits with what appears to be a difference in outcomes, a difference in treatment approaches, and in the mechanism of spread. Furthermore, this is consistent with the classification system for lung cancer.

The TD-SPFC faced certain limitations in developing a stage classification scheme. Despite the unprecedented size of the retrospective database that was assembled, the size of subgroups rapidly becomes smaller as one tries to examine more nuances. The relative paucity of data on patients not resected compounds this issue in patients with more advanced tumors—such as those in which the N and M components are prominent. Furthermore, the advanced disease patients for whom data is available represent a skewed cohort, hampering the utility and validity of analyzing differences in outcomes. Finally, as in any retrospective database, there is missing data and lack of clarity in how details were defined at the source institutions.

However, we must remember that the purpose of stage classification is to develop a useful nomenclature. Considering outcomes is only a tool to accomplish this; furthermore, the observations must be interpreted with clinical insight into the entire spectrum of factors that affect outcomes—the anatomical extent of disease being only one factor that in some situations may contribute relatively little. The TD-SPFC sought to consider all factors not only the analysis of outcomes.

The proposed stage classification is only a step in an ongoing process. ITMIG has initiated prospective data collection which is much more detailed. Furthermore, the TD-SPFC will begin development of a prognostic prediction model. These initiatives should foster further progress in the future. In the meantime, the TD-SPFC hopes that the proposed classification will be found to be useful in providing a consistent language that facilitates collaboration around the world.

CONCLUSION

The proposals for the N and M components of stage classification in thymic malignancies described in this article represent the output of an initiative conducted by IASLC and ITMIG to develop a uniform official classification system that facilitates communication and collaboration around the world. This work was conducted over the course of 4 years, and involved extensive analysis of a large worldwide database, as well as consideration of clinical and practical factors. Together with proposals for T classification and stage grouping, this provides a solid basis for stage classification of thymic malignancies.

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APPENDIX 1. IASLC STAGING AND PROGNOSTIC FACTORS COMMITTEE

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APPENDIX 2: ADVISORY BOARD OF THE IASLC THYMIC MALIGNANCIES DOMAIN

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APPENDIX 4: ADVISORY BOARD OF THE IASLC ESOPHAGEAL CANCER DOMAIN

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